Lyme disease

\[\text{not as common or fatal as RMSF, esp in Ky.}\]

*Borrelia burgdorferi*

*At least 20 spp. or so.*

Many researchers have subdivided this species. All Lyme disease spirochetes constitute "*B. burgdorferi sensu lato*," and include *B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelii*, *B. japonicum*, *B. turdi*, and many, many more.

Other researchers consider their differences trivial and call them all *B. burgdorferi.*

All these bacteria can cause Lyme disease. → look alike or similar spp.

Lyme disease primarily occurs in the northeastern US and around the Great Lakes.

Rare in Kentucky & also coastal Oregon/CA = dep. on spp. & what they feed on

Ground Hog Tick → doesn't feed on humans.

Approx. 18,000 cases annually in US (but prob. much more)

*very mis-diagnoses over & under.*

Rare fatal cases due to heart block (less than a dozen confirmed deaths since Lyme disease was recognized in late 1970s)

Spread by *Ixodes* spp. ticks:

*I. scapularis* (*I. dammini*) in eastern US (deer tick or black-legged tick)
*I. pacificus* in western US (also called black-legged tick)

These ticks can also transmit *Anaplasma (Ehrlichia)* and *Babesia*, so consider co-infections.

Other *Ixodes* spp. may harbor *B. burgdorferi*, but rarely feed on humans and so not much of a threat.

NO evidence that any other types of tick can transmit *B. burgdorferi*
NO evidence that any other arthropod (e.g. mosquitoes, biting flies) can transmit *B. burgdorferi*
In endemic areas, nymphal feeding precedes larval feeding. Creates high infection rate in mice, therefore a high chance of larvae acquiring infection.

In non-endemic areas where vector ticks are found, larvae and nymphs prefer to feed on animals that are not competent for *B. burgdorferi* infection, such as lizards in California and southern US.

Bacteria found only in midgut ("stomach") of unfed ticks

Ticks feed for several days

Migrate to salivary glands only after tick begins feeding, takes approx. 2 days

Therefore, a tick removed within 48 hours of infection is unlikely to transmit *B. burgdorferi*

Lyme disease is most often transmitted by the nymph stage, frequently unnoticed due to small size

Adults are usually noticed early and removed before transmitting *B. burgdorferi*

Larvae are small, but are not infected with *B. burgdorferi*
**B. burgdorferi** virulence factors

Several identified surface proteins bind extracellular matrix components (decorin, fibronectin, etc.), possibly facilitate adherence of bacteria to extracellular matrices.

Several different surface proteins bind host complement inhibitor \( \text{Factor H} \), protect against alternative pathway of complement. *very resistant to serum/all pathway*

\( \text{VlsE}: \) surface protein, sequence varies during infection

*infxs close = 10 bact.*

**Symptoms of Lyme disease:** all appear to be due to immune system responses.

Vary widely between patients. *mice do not get s/o of human*

Flu-like illness initially

\( \leftarrow \) Erythema migrans (EM or ECM): "bulls-eye" rash \( \geq 5 \text{ cm} \) in diameter around bite. *Painless wound.* 

→ dissemination of bact through skin & tissues \( \rightarrow \) not transmitted w/ blood!

Expands over time, self resolving.

Appears in most, but not all, cases.

Caused by inflammation due to spirochetes disseminating through skin tissue. Fluid-filled vesicles occasionally observed in EM.

Self-resolving

**Presence of EM is diagnostic for Lyme disease.**

Bacteria disseminate throughout body, primarily by migration through skin and other tissues. Little to no spread through bloodstream. *spread extraceli*

Bacteria establish persistent infection of many tissues. *many yrs production*

Extracellular

Often associated with collagenous tissues. *immune sys. will NOT totally clear infxn.*

Bacteria repress expression of many surface proteins

Gene encoding outer surface protein \( \text{VlsE} \) undergoes recombination, novel \( \text{VlsE} \) variants expressed

Become dormant?

A variety of later-stage symptoms possible. Some, all or none may develop
Early disseminated symptoms
(weeks to months after tick bite) stems:

Neurologic problems (neuroborreliosis) -
Bell’s palsy (paralysis of facial nerve), sometimes only one side → in Ky, most likely NOT Lyme DZ
In endemic areas, this is highly suggestive of Lyme disease.
Meningitis
Encephalitis
Other neuropathies

Cardiac problems
Conduction deficits: AV nodal block may require pacemaker
Myocarditis
Pericarditis *rare, but only cause of Lyme dz death.

Late disseminated symptoms
(months to years after tick bite) Inflammatory arthritis -
Generally in a large joint, with knee or elbow most common. (not fingers or toe)
Often only one side affected

No credible evidence that B. burgdorferi causes Alzheimer’s disease, multiple sclerosis, ALS, lupus, or any other chronic disease.

Diagnosis of Lyme disease

Clinical diagnosis is mandatory, since testing is far from perfect. *high rate of false(+) & false(-)

Presence of EM is diagnostic, no testing is required.

History of tick bite associated with other characteristic manifestation of Lyme disease increases probability of this being the cause. (see NIAID handout)

*NOT dx for lyme dz
Prolonged malaise, nausea, headache, memory loss, confusion, attention deficit, generalized body aches, stiff muscles, or arthritis of small joints alone are NOT indicative of Lyme disease (although you will probably meet patients with such symptoms who swear they have Lyme disease and will demand to be treated).

Serologic tests are never to be used alone for diagnosis of Lyme disease, only as part of diagnosis of probable cases (see attached FDA bulletin).
Many uninfected people will test positive due to cross-reactivity with antibodies produced against other bacterial infections:
- flagella of oral treponemes,
- heat shock proteins of all bacteria are well conserved

ELISAs are simple and cheap. Most use bacterial lysates as target, so have high false positive rate (due to cross-reactivity from antibodies directed against flagella of oral spirochetes).

A positive ELISA that used a bacterial lysate must be followed up with more specific test, such as Western blot (immunoblot)

This “two-tier” testing is recommended by CDC and other authorities

Be aware that patients will probably be confused by positive ELISA followed by negative Western blot. Be sure to explain why this happened.

Internet chat rooms and support groups are filled with people who believe they have Lyme disease but were ignored, improperly treated or misdiagnosed by their physicians. Many had positive ELISA tests followed by negative Western blots.

There is also considerable sequence variation among antigens produced by different *B. burgdorferi* during mammalian infection.

Different companies use different reference material, and results often vary depending upon test kit used.
New, single-step test being marketed using ELISA with a conserved region of VlsE ("C-6 Test")

Still being tested for sensitivity and specificity

If this test works, it should eliminate or reduce problems associate with "two-tier" test

Skin biopsies taken near the edge of EM, or blood taken at time of EM can sometimes be successfully cultured for B. burgdorferi. This is difficult, expensive, and not worth doing since EM is diagnostic for Lyme disease.

PCR of tissue biopsies is sensitive, but very inaccurate. In one study, a very large proportion of reported "positives" were actually due to amplification of DNA from another source (i.e., not B. burgdorferi DNA)

Some companies are marketing services to culture patient blood, examine urine for B. burgdorferi antigens (LUAT), or perform neurological tests. No evidence that any of these work, and they should be considered bogus.

*Almost always look positive, esp w/ correct hx.*

Treatment of Lyme disease:

B. burgdorferi are very sensitive to β-lactams and tetracyclines, as are all spirochetes

Use of tetracyclines has added benefit of also being effective against Ehrlichia coinfections

3-4 weeks oral therapy is normally effective.

Infections that have persisted for a long time may require 1 month or so of I.V. antibiotics.

No credible evidence that longer term (>1 month) antibiotics have any effect.

Some other antibiotics are occasionally used, but have not been well tested.

B. burgdorferi are naturally resistant to rifampin, sulfonamides, phosphomycin.

*Symptoms may not resolve even with clearance of infecting organisms. Sometimes damage is irreversible.*
Lyme disease vaccine:
Off market since spring 2002
Used recombinant form of OspA, an outer surface protein

• Required multiple, yearly vaccinations

• Worked by very inefficient mechanism
  *Kneaded high-enough titer to sterilize the tick

• Linked to autoimmunity

So far, every protein identified that is produced by
*B. burgdorferi* during mammalian infection varies considerably between different bacteria, and has been useless as protective vaccines.

Southern Tick-Associated Rash (STAR, STARI, Master's Disease)
also called "STARI" or "Master's disease"

Erythema migrans-like rash surrounding arthropod bite wound

Outside endemic Lyme disease areas
  (mostly southern US, including Kentucky)

No serologic evidence of *B. burgdorferi* infection
  → NO CROSS-REACT OR SEROCONVERSION

Speculated to be caused by a non-Lyme disease* Borrelia*

Recommended antibiotic treatment same as for Lyme disease.

Recently cultured (2004) spirochete, *Borrelia lonestarii*, has been found in lonestar ticks
  (*Amblyomma americanum*).

Not known whether *B. lonestarii* causes STAR

He Tx is same as Lyme Dz, just dx as Lyme Dz.
Tick-borne Relapsing Fever (Endemic RF)

Primarily in western, southwestern and occasionally southeastern US. May be in KY

Occasionally fatal

Several species of *Borrelia*, each specifically transmitted by a species of *Ornithodoros* tick. Include *B. hermsii*, *B. parkeri* and *B. duttonii*.

*Ornithodoros* spp. ticks are soft ticks, look and behave very differently from the hard ticks you are probably familiar with. Soft ticks are fast feeders, completing a blood meal in 15-30 min. People are commonly infected when sleeping in rodent-infested cabins, ticks come out to feed at night. These ticks feed many times during their lives (ticks may survive for many years).

Bacteria migrate to tick salivary glands within days of tick infection, are transmitted as soon as the tick begins feeding again.

Bacteria replicate to high levels in mammalian blood, which causes fever, malaise, etc. Bacteria can often be seen in Giemsa stained blood smears.

Bacteria disappear from blood after a few days, then reappear several days later.

Characterized by periods of fever broken by periods of normalcy (similar to malaria)

Relapses recur until immune system finally clears infection

![Figure 1](image)

*Figure 1:* Body temperature over 8 weeks of a patient with relapsing fever. The patient was infected with the tick-borne relapsing fever agent, *B. hermsii*.

Bacteria during each relapse produce a different surface protein - VMP (variable membrane protein). Variation occurs by recombination mechanism (see notes from my lectures earlier in IID)
Louse-borne Relapsing Fever (Epidemic RF)

One species, \textit{B. recurrentis}, genetically very similar to agents of TBRF

Spread by human body louse (same vector as epidemic typhus)

Endemic in highlands of Ethiopia

Transmitted when louse is crushed and body fluids enter wound in skin

Symptoms similar to TBRF

LBRF fatality rate much greater than TBRF, possibly due to general health of patient.
Treatment of Relapsing Fevers

Tetracyclines or β-lactams both work well, but tetracyclines are preferred for quicker clearance of bacteria.

Treatment during bacteremia phase may cause intense reaction due to sudden release of endotoxins (bacterial constituents) - Jarisch-Herxheimer Reaction.

**J-H Rxn can be fatal!**

Close observation of patient during treatment is important.

J-H may be reduced by accompanied treatment with hydrocortisone and acetaminophen.

Leptospirosis

*Leptospira interrogans*

Some researchers have divided *L. interrogans* into several species, with considerable genetic differences among these species. There are many serovars and types.

A large degree of specificity for certain serotypes to infect certain animals.

E.g. in the Lexington area, horses are most frequently infected with serotype *pomona* type kennewicki

**Specificity correlates with LPS (or LPS-like substance) on surface, probably because of interactions with host tissues.**

Many wild and domestic animals carry *L. interrogans* asymptotically

Shed in urine of carrier animals → goes to kidneys → may cause kidney problems.

Enter body through skin or mucous membranes.

Humans become infected by contact with urine or urine-contaminated water/soil

- Rat urine in inner cities
- Also rat urine in coal mines
- Contaminated lakes & ponds. Recent outbreaks occurred after triathlons, racers were infected during swimming section of race.
- Endemic in many tropical and semitropical countries.
- Rainy season = Leptospirosis season in Central America

Infection primarily of kidneys and liver, but other organs can be infected (e.g. eyes)

*Jaundice & other problems.*
Many infected persons are asymptomatic (carriers)

~90% of patients exhibit anicteric phase
  "flu-like" symptoms - headache, fever, chills, nausea, vomiting, myalgia
  meningitis occasionally occurs
  resolve within 1-3 weeks as antibodies accumulate

~10% of patients exhibit severe leptospirosis (Weil's syndrome)
  jaundice
  renal dysfunction
  spontaneous bleeding
  high fatality rate

An especially virulent strain of *Leptospira* has recently been seen in Brazil and other tropical/semitropical countries *very high fatality*

Severe pulmonary form of leptospirosis (SPFL)

organs, especially lungs, spontaneously hemorrhage
numerous fatalities

*Diagnosis generally by serology*

*Treatments:*
  Oral *-lactams or tetracyclines for mild cases
  IV for more severe cases may be warranted*